2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.

Remarks

Applicants have amended the specification to update the priority data of this application. The application has been amended to reflect that U.S.S.N: 09/371,747, filed on August 8, 1999, has now issued as U.S. Patent No. 6,395,716.

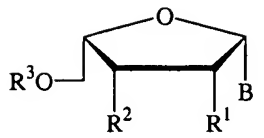
Claims 13-61 and new claims 63-67 are now pending and are directed to methods to treat hepatitis B virus in a human using β-L-2'-deoxycytidine and/or β-L-thymidine.

Enclosed hereto is a marked up version of the changes made by the current amendment, in accordance with 37 CFR §1.121 (c). The enclosed page is captioned "**Version with Markings to Show Changes Made**."

An assignment was filed on May 24, 2002 with the Patent Office, in which the Centre National de la Recherche Scientifique assigned its rights in this application from Jean-Louis Imbach to L'Université Montpellier II (UMII). A copy of the assignment is enclosed.

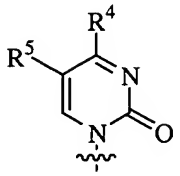
Rejections under 35 U.S.C. § 102 and 103

Original claims 13-62 were rejected under 35 U.S.C. § 102(b) on the basis that European Patent Application No. 0 352 248 A1 ('248) to Johansson et al. (the Medivir application) discloses the nucleosides of the present invention for the treatment of hepatitis B. The Examiner is respectfully requested to reconsider this rejection in light of the claims now presented, which are directed to the use of β-L-2'-deoxycytosine and β-L-thymidine. The '248 patent discloses L-ribofuranosyl compounds which include analogs of the formula **I**:



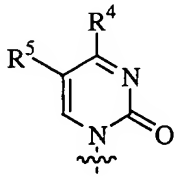
(I)

wherein R^1 and R^3 can be hydrogen, R^2 can be OH and B is adenine, guanine, hypoxanthine, 2,6-diaminopurine or



wherein:
R^4 is OH or NH_2, and
R^5 is H, CH_3 or C_2H_5.

However, there is an express limitation in the disclosure of the '248 specification and claims which states that when the nucleoside is the β anomer, R^1 is H, R^2 is OH, and R^3 is OH, B is limited to adenine, guanine, hypoxanthine, 2,6-diaminopurine or



wherein
R^5 is C_2H_5 when R^4 is OH and
R^5 is CH_3 or C_2H_5 when R^4 is NH_2;

Therefore, in the '248 patent, B specifically **cannot** be thymine or cytosine, because the Medivir text specifically excluded it. The only portion of the entire publication that specifically mentions the claimed β-2'-L nucleosides is in the prior art section where they cite Holy et al. Coll. Czech. Chem. Commun., **1972**, *37*, 4072-4087 for syntheses of β-L-thymidine and β-2'-deoxy-L-cytidine.

Original claims 13-62 were rejected under 35 U.S.C. § 103(a) as obvious in light of the combination of European Patent '248 with von Janta-Lipinski et al. J. Med. Chem., **1998**, *41* (12), 2040-2046. As discussed above, the claims as now presented are not disclosed, and in fact, are explicitly excluded from '248 patent. The von Janta-Lipinski reference discloses that the

triphosphate of β-L-thymidine (but not β-L-2'-dC) is a substrate for the DNA polymerases of HBV and DHBV. However, only triphosphorylated β-L-thymidine was evaluated, not the unphosphorylated form, and there is no comment in the article on whether those β-L-nucleosides are phosphorylated in cells or *in vivo* or, more importantly, there is no comment on the efficacy of phosphorylation of β-L-thymidine *in vivo*. In order for a nucleoside to be active against the hepatitis B virus, the nucleoside (i.e. β-L-2'-deoxythymidine, L-dT) first must be phosphorylated by an enzyme in the cytosol to the monophosphate (i.e. β-L-2'-deoxythymidine monophosphate, L-dTMP), then the monophosphate must be phosphorylated by an enzyme in the cytosol to the diphosphate (i.e. β-L-2'-deoxythymidine diphosphate, L-dTDP), then the diphosphate must be phosphorylated by an enzyme in the cytosol to the triphosphate (i.e. β-L-2'-deoxythymidine triphosphate, L-dTTP). Because of this, the article does not teach one of skill in the art that β-L-thymidine would have any hepatitis B activity in a cell or *in vivo*.

Further, as scientists of skill in this art are aware, one cannot effectively administer a triphosphate of a nucleoside in vivo, because it is readily dephosphorylated in biological fluid to the free unphosphorylated form, and then has to be converted back to the active triphosphate form in vivo by intracellular kinases.

The prevailing data at the time, reported by Spadari, et al. ("L-Thymidine is Phosphorylated by Herpes Simplex Virus Type 1 Thymidine Kinase and Inhibits Viral growth," J. Med. Chem., **1992**, *35*, 4214-4220, copy enclosed), indicated, although incorrectly, that while β-L-dT was a substrate for herpes simplex thymidine kinase, it was not a substrate for human thymidine kinase. On the basis of the Spadari article, scientists believed at the time that β-L-dT would not be phosphorylated in a cell-based system or *in vivo*. Thus, the combination of the von Janta-Lipinski and Spadari taught at the relevant time that while the triphosphate of β-L-dT is an inhibitor of HBV DNA polymerase in a laboratory cell-free environment, the triphosphate is not produced inside the cell because it is not a recognized substrate for cellular kinases, and thus the parent unphosphorylated compound would be useless in a cell or *in vivo* since it couldn't be activated.

The scientific and patent literature is filled with examples of synthetic nucleosides that in a triphosphorylated form are able to inhibit a polymerase or reverse transcriptase, but have little

or no activity *in vivo* because of either the inability of the synthetic nucleosides to be effectively phosphorylated in the body, or because they are metabolized in a manner that doesn't allow the triphosphorylated form to exist long enough to have a therapeutic effect. Because of this, one could not have predicted or even had a reasonable assurance of *in vivo* activity from the *in vitro* inhibition of an enzyme when presented artificially in the activated state under laboratory conditions.

The correlation between antiviral activity of a nucleoside triphosphate in an *in vitro* polymerase assay and prediction of antiviral activity in cell-based assays or *in vivo* against a replicating virus such as HBV was not established in the von-Janta-Lipinski article. To the contrary, the authors recommended further evaluation of the chemical compound β-L-FTdR as a selective inhibitor of HBV, which as a synthetic triphosphate derivative (β-L-FTTP) was the most active against the HBV and duck polymerases. However, β-L-FTdR has now also been shown to be inactive against the replicating virus in cell-based systems or *in vivo* (Bryant, et.al. "Antiviral L-Nucleosides Specific for Hepatitis B Virus Infection," Antimicrobial Agents and Chemotherapy **2001**, *45*, 229-235).

von Janta-Lipinski et al filed a patent application on the work described in the J. Med. Chem. article, that claimed only the 3'-deoxy-3'-fluoro-β-L-nucleosides and β-L-arabino-nucleosides, but intentionally omitted β-LdT (and β-LdC), for the treatment of hepatitis B (International Patent Application, WO 96/11204).

The Background of WO 96/1204 application stated that:

L-nucleosides, the enantiomers of naturally occurring D-nucleosides, have long been deemed not enzymatically metabolizable and hence ineffective in biologic systems. A break with this dogma was made in 1992 by the findings of Spadari et al., who showed that **while β-L-thymidine is not converted by cellular TdR kinase**, a substrate of the corresponding enzyme of Herpes simplex virus 1 is (Spadari et al., J. Med. Chem. 1992, 35, 4214-4220). In the period following, a variety of β-L-nucleoside analogs, such as for example: β-L-didesoxycytidine (L-ddC) (M. Mansuri et al., Bioorg. Med. Chem. Lett. 1991, 1, 65-68), β-L-5-fluorodidesoxy-cytidine (L-FddC) and β-L-5-fluorodidesoxyuridine (L-FddU) (T.-S. Lin et al., J. Med. Chem. 1994, 37, 798-803), β-L-3-thiacytidine (L-3TC) (C. N. Chang et al., J. Biol. Chem. 1992, 267, 22414-22420) and β-L-5-fluorothiacytidine (L-FTC) (P. A. Furman et al., Antimicrob. Agents Chemother. 1992, 36, 2686-

2692) were prepared in pure form or purified. These compounds were compared with the corresponding enantiomers with respect to their antiviral activity on HBV and HIV replication and their antiproliferative toxicity.

(English translation of German text, copy enclosed)

Thus, von Janta-Lipinski et al. apparently thought that although the triphosphate of β-L-thymidine is a substrate for HBV DNA polymerase *in vitro* it would be ineffective *in vivo* because it is not phosphorylated by thymidine kinase, citing to Spadari, and thus omitted β-L-dT (as well as β-L-dC) from the invention.

Art cited in corresponding European Patent Application No. 99941027.7

Lin et al. "Synthesis of Several Pyrimidine L-Nucleoside Analogues as Potential Antiviral Agents" Tetrahedron, **1995**, *51* (4), 1055-1068 (D1), discusses that β-L-5-iodo-2'-deoxyuridine (β-L-IUdR, compound **7**) is active against herpes infection and various other DNA viruses, that BVdU and β-L-BV-ara-U are also active against herpes, β-L-BV-ara-U is active against varicella-zoster virus; and that 2',3'-dideoxy-β-L-azacytidine was found to be active against HBV. The reference teaches away from the use of β-L-dT to treat hepatitis B where it notes that Spadari et al reported that β-L-dT is not recognized by human thymidine kinase (and by inference thus that it would not be considered to be phosphorylated to the active triphosphate in the cytosol in vivo, see further discussion below). See Lin, page 1055. This references does not disclose the method to treat hepatitis B with β-L-2'-deoxycytosine or β-L-thymidine.

Canadian Application No. 2,206,878, corresponding to WO 97/11087 (D2), and WO 99/45935 (D3) to Weis teach the use of certain dinucleoside dimers that contain at least one L-sugar primarily for the treatment of tumors. The specifications do not teach or suggest that the nucleosides in the present use claims are active in non-dimeric form, and on the contrary, teach that it is the dimeric form that exhibits the activity. The Background of the Invention for example points out that types of nucleoside dimers are naturally synthesized as part of the manufacture of DNA oligomers in the body (page 1 of '878). The Background further states that "Thus, L-nucleoside-based compounds have potential as drugs against neoplastic and viral

diseases. While L-sugar derived nucleosides and their oligonucleotides have been widely evaluated for such activities, little is known regarding the biological activities of shorter oligomers such as dimers obtained by :L-nucleoside substitution."

Prior to the filing date of the Weiss applications, it had been affirmatively reported by the Yale University School of Medicine that β-L-dT has no activity against hepatitis B in whole liver cells transfected with hepatitis B. (Lin et al. J. Med. Chem., **1994**, *97*, 798-803, copy enclosed, which reported that β-LdT reportedly showed no activity when tested at up to ten micromolar in HBV transfected immortalized human hepatoma cells *in vitro* (see Table 2)).

Further, these Weiss references primarily focus on the treatment of tumors. The only disclosure in D2 directed to the treatment of viral diseases is the following:

> "A further embodiment of the present invention is the administration of a therapeutically effective treatment amount of the compounds of the present invention for the treatment of cancer or viral infections."
>
> page 7, lines 13-16

Similarly, the only disclosure in D3 directed to the treatment of viral diseases is the following:

> "A further embodiment of the present invention is the administration of a therapeutically effective treatment amount of the compounds of the present invention for the treatment of cancer , viral infections, parasitic infections, fungal infections, and bacterial infections."
>
> page 6, lines 20-23

These statements do not specifically disclose the use of β-L-dT or β-L-dC for the treatment of HBV in particular. The term "hepatitis B" is not used in the Weiss specifications. Any assumption that this generic disclosure of compounds for the treatment of "viral disease" implicates the use of a compound treat HBV in particular: (i) ignores fundamental differences between cancer, parasitic infections, fungal infections, bacterial infections and viral infections, and even the fundamental differences between viral families; and (ii) is contrary to experience in the nucleoside art area generally.

For example, numerous nucleosides exhibit biological activity (i.e. exhibits EC_{50}'s of less than 10 μM) against other viruses (such as HIV) but not hepatitis B, or vise versa.

(a) AZT inhibits HIV but not hepatitis B;

(b) D4T (β-D-2',3'-dideoxy-2',3'-didehydrothymidine) inhibits HIV but not hepatitis B;

(c) CS-92 (β-D-3'-azido-2',3'-dideoxy-5-methylcytidine) inhibits HIV but not hepatitis B;

(d) CS-87 (β-D-3'-azido-2',3'-dideoxy-uridine) inhibits HIV but not hepatitis B;

(e) MKC-422 inhibits HIV but not hepatitis B;

(f) Nervirapine inhibits HIV-1 but not hepatitis B;

(g) L-FMAU inhibits hepatitis B but not HIV;

(h) Famciclovir inhibits hepatitis B but not HIV;

(i) Penciclovir inhibits hepatitis B but not HIV;

(j) FTC is active against HIV and HBV but no other known virus; and

(k) β-LdT and β-LdC are active against HBV but no other known virus, including HIV.

A statement that a compound has "antiviral activity" is neither a disclosure that it has activity against all viruses or a disclosure of one in particular unless it is mentioned. Applicant is aware of few or no universal antiviral agents.

D2 and D3 do not provide any specific data for the use of the compounds for the treatment of any particular viral disease, such as HBV. Rather all the examples focus on the use of the β-L-2'-deoxynucleosides, such as β-L-2'-deoxyinosine, or L-nucleoside dimers for the treatment of neoplastic diseases, and in particular melanoma and leukemia, or a parasitic infection, and in particular a *P. falciparum* (FCQ27) infection.

Discussion of Additional References

The Examiner's attention is directed to the following references, copies of which are enclosed.

As the Examiner may be aware, when administered to cells, a nucleoside disperses through the cell into the cytosol and the mitochondria. The mitochondria is separated from the cytosol by a mitochondrial membrane. It has been known by scientists for a long time that there

is a nucleoside kinase in the cytosol that acts on thymidine (thymidine kinase 1 or TK1) and a separate nucleoside kinase in the mitochondria that acts on thymidine (thymidine kinase 2 or TK2). When a cell is infected with hepatitis B, the viral replication takes place in the cytosol. It has been reported that nucleosides that are triphosphorylated in the mitochondria are trapped by the membrane and cannot get back in to the cytosol (see Zhu, discussed below). Therefore, to exhibit hepatitis B activity, the nucleoside must be recognized as a substrate by an enzyme in the cytosol such as TK1 to be monophosphorylated in the cytosol, and then further recognized by the appropriate enzymes in the cytosol to be di- and tri-phosphorylated in the cytosolic compartment which then is presented to and inhibits the cytosolic hepatitis B viral polymerase.

Spadari, et al. ("L-Thymidine is Phosphorylated by Herpes Simplex Virus Type 1 Thymidine Kinase and Inhibits Viral growth," J. Med. Chem., **1992**, *35*, 4214-4220), as discussed above, disclosed, that while β-L-dT was a substrate for herpes simplex thymidine kinase, it was not a substrate for human thymidine kinase. On the basis of the Spadari article, scientists believed at the time that β-L-dT would not be phosphorylated in the cytosol of a cell-based system or *in vivo*.

Jurovčik and Holý "Metabolism of pyrimidine L-nucleosides," Nucleic Acids Research, August 1976, 3(8), 2143-2153 discusses the distribution of L-cytidine, L-uridine and L-2'-deoxythymidine within various tissues in mice and demonstrated that L-2'-deoxythymidine is minimally phosphorylated in the liver of mice, but does not address by which enzyme or in which part of the cell, because they looked at tissue homogenates. Mice are not carriers of the hepatitis B virus.

Verri et al. Biochem J. **1997**, *328*, 317-320, reported that while cytosolic thymidine kinase does not phosphorylate β-L-thymidine (positively referring to Spadari, et al.), mitochondrial thymidine kinase can phosphorylate β-L-thymidine, which appears to be consistent with Holy's finding in mice. However, as discussed above, it has been reported that mitochondrial nucleoside triphosphate pools are sequestered by the mitochondrial membrane and cannot enter the cytoplasmic pool where *de novo* deoxyribonucleotide synthesis occurs (Bestwick et al., J Biol Chem, **1982**, *257*, 9300-9304; Berk et al., J Biol Chem, **1973**, *248*, 2722-2729; Davis et al., J Cell Biol, **1996**, *135*, 883-893). Later studies by Zhu et al., J Biol Chem,

2000, *275*, 26727-26731 supported this position, showing that, in a cell model system, nucleoside analogs phosphorylated to the nucleotide triphosphates in the mitochondria are trapped in the mitochondiral compartment and cannot enter the cytosol. These papers by implication correct speculative comments in a review by Arnér et al. Pharmac. Ther., **1995**, *67* (2), 155-186, which suggests the possibility that nucleosides phosphorylated in the mitochondria might escape to the cytoplasm. Based on the finding that [^{3}H]-thymidine leaked from mitochondria are being utilized for subsequent incorporation into DNA of resting cells, Arnér et al. state that "[t]here is most likely an exchange of deoxynucleotides between the mitochondrial matrix and cytoplasm. ... TK2 phosphorylates Thd, after which transport of TMP, TDP and TTP to the cytosol must occur." However, these statements were speculative with no supportive data, and are rebutted by the work of Bestwick, Berk, Davis and Zhu.

Verri et al. Mol. Pharmacol. **1997**, *51* (1), 132-138, reports that while cytosolic thymidine kinase does not phosphorylate β-L-thymidine (referring again to Spadari, et al.), 2'-deoxycytidine kinase is relatively less enantioselective, and was shown to monophosphorylate β-L-2'-deoxycytidine ("β-LdC"). However, prior to the Verri publication and also prior to the present priority date, there had been no disclosure that β-LdC triphosphate is a substrate for hepatitis B polymerase. In addition, no data had been reported regarding the phosphorylation of β-L-2'-deoxythymidine by 2'-deoxycytidine kinase. Further, no reference had reported whether the monophosphate of β-L-2'-deoxycytidine could be di- or tri-phosphorylated in the cytosol.

The Examiner's attention is also directed parenthetically to two Russian articles that appear to erroneous cite Spadari: Krayevsky et al. Molecular Biology, **1996**, *30* (5, part 1), 585-591 and Krayevsky et al. J. Bimolecular Structure & Dynamics, **1996**, *14* (2), 225-230. These articles erroneously report that Spadari states that L-dT is phosphorylated by thymidine kinase, thymidylate kinase and nucleoside diphosphate kinase. They state that because L-thymidine "inhibits short-term incorporation of exogenous [^{3}H]thymidine into cell DNA; this means that L-thymidine blocks D-dTTP synthesis via an additional metabolic route involving thymidine kinase, thymidylate kinase and nucleoside diphosphate kinase." (See Table 1 and its footnote in both references.) However, Spadari et al. clearly teaches the opposite, that LdT, LdC, LdA, LdG and LdU are not substrates for **human** thymidine kinase. In the first paragraph on page 4217, Spadari et al. states that L-thymidine selectively inhibits [^{3}H]thymidine into **HSV1-TK**

transformed HeLa cells without effecting cellular growth and viability. "L-T ... inhibits the utilization of [^{3}H]T only in the cell line which depends on viral TK for T incorporation." Therefore, Spadari et al. teaches that in this system, LdT is phosphorylated **only** by HSV TK in transfected cells and **not** in wild type cells (HeLa).

The Examiner's attention is also directed to Söderlund et al. Purine and Pyrimidine Metabolism in Man VIII, edited by A. Sahota and M. Taylor, Plenum Press, New York: **1995**, 201-204. This reference describes the possibility that TK2, the mitochondrial TK, is present in the cytosol as well as the mitochondria. Again, these statements are merely speculative and were not confirmed. This supposition is based only on the fact that dC phosphorylation occurs in the mitochondria and cytosol of dCK$^-$ cells. However, while the phosphorylation of thymidine was readily detected in the mitochondria of TK1$^-$ cells, **no phosphorylated thymidine was found in the cytosol** (reflecting the necessity of TK1 for thymidine phosphorylation in the cytosol). These findings actually suggest that despite the fact that there was phosphorylation of dC in the cytosol in dCK$^-$ cells, there is no TK2 present in the cytosol, because there was no phosphorylation of thymidine in the cytosol in TK1$^-$ cells.

Further, Verri et at., Biochem J, **1997**, *328*, 317-320, demonstrates that LdT phosphorylation by TK2 could not have been anticipated *in vivo*. Thymidine phosphorylation by TK2 is preferential for the D-form over the L-form. Thus, LdT is not as good a substrate for TK2. The role of TK2 in phosphorylation of LdT is negligible because the preferential phosphorylation of thymidine, even in the presence of high concentrations of LdT, coupled with the higher K_m for LdT, makes TK2 resistant to LdT. This would, in effect, minimize any contribution of TK2 to the phosphorylation of LdT in the cytosol.

The repeated reference by scientists over a number of years to Spadari's observations that β-L-deoxythymidine ("β-L-dT") is not phosphorylated in the cytosol in a cell-based system or *in vivo* confirms the acceptance of this observation by those of skill in the art at the time. See for example Verri et al. "Relaxed enantioselectivity of human mitochondrial thymidine kinase and chemotherapeutic uses of L-nucleoside analogues" Biochem J. **1997**, *328*, 317-320; Verri et al. "Lack of Enantiospecificity of Human 2'-Deoxycytidine Kinase: Relevance for the Activation of β-L-Deoxycytidine Analogs as Antineoplastic Agents" Mol. Pharmacol. **1997**, *51* (1), 132-138;

Lin et al. "Synthesis of Several Pyrimidine L-Nucleoside Analogues as Potential Antiviral Agents" Tetrahedron, **1995**, *51* (4), 1055-1068; and WO **96/**11204.

To summarize: prior to the present priority date,

- β-LdT in the triphosphorylated form was known to be a substrate for hepatitis B polymerase in a cell free laboratory test tube environment, but as the free nucleoside was thought not to be significantly phosphorylated in the cytosol in vivo, and thus not capable of being effectively converted into the active triphosphate form in vivo;
- β-LdT was reported by leading international antiviral scientists at Yale University School of Medicine to have no activity when tested in vivo in hepatitis B transfected immortalized human liver cells; and
- β-LdC was known to be phosphorylated to the monophosphate in the cytosol in vivo, but it was not known whether it would be phosphorylated to the triphosphate in the cytosol in vivo or whether it was a substrate in the triphosphate form for hepatitis B viral polymerase.

The Applicants of the present invention discovered that von-Janta-Lipinski was wrong. β-L-dT is a substrate for two cellular kinases, deoxycytidine kinase and thymidine kinase 1 with subsequent activation to the triphosphate derivative in human hepatocytes in vivo. The Applicants of the present invention also discovered that Yale University Medical School (Lin) was wrong. β-L-dT when phosphorylated in hepatitis B infected liver cells is a highly potent anti-HBV agent. Instead of anticipating or rendering obvious the present application, the von-Janta-Lipinski and Lin references support the patentability of the claim for the use of β-L-dT to treat HBV infection.

In fact, β-L-dT is now in advanced clinical trials by Idenix Pharmaceuticals, Inc. for the treatment of hepatitis B in a number of cites around the world, and has demonstrated superior in vivo therapeutic effects. It is scheduled to be the second or third small molecule approved in the world for the treatment of hepatitis B. An amino acid ester of β-L-dC is likewise in clinical

trials. The Examiner is encouraged to visit www.idenix.com to learn more about these drugs and their development.

Rejections under 35 U.S.C. § 112

The Examiner rejected originally pending claims 16-17 and 40-62 under 35 USC 112, first paragraph, allegedly because the administration of L-nucleosides with one or more other antiviral agents is not enabled. On the contrary, combination and alternation therapies are described throughout the specification and are well understood to those of skill in the art. In particular, combination and alternation therapies of the present invention are described in detail on page 17, line 1 to line 26. Method for the pharmaceutical administration of the compounds is also described in detail in the specification and clearly teach the reader how to practice the invention. Further, combination therapy is the standard of care in HIV therapy and is well understood and practiced by those in the field of antiviral therapy.

Original claims 16, 17, 42 and 53 were rejected under 35 U.S.C. §112, second paragraph, allegedly because the term "arabinofuranolyl" is indefinite. According to the Examiner's suggestion, Applicants have amended the present claims to clarify the term "arabinofuranolyl" as "arabinofuranosyl."

Original claims 13-14, 16-17 and 40-61 were rejected under 35 U.S.C. §112, second paragraph, allegedly because the claims are grammatically incorrect. Applicants have amended these claims according to the Examiner's suggestions.

Objections under 37 C.F.R. § 1.75(c)

Original claim 39 was objected to under 37 C.F.R. § 1.75(c) allegedly because the multiple dependent claim depended improperly on another multiple dependent claim. Applicants have amended the claim such that it properly depends on dependent claims 37 and 38.

Double Patenting Rejections

Claim 62 was rejected under the doctrine of statutory anticipation-type double patenting in light of the claims presented in U.S.S.N. 09/371,747, now U.S. Patent No. 6,395,716 ('716). Applicants have cancelled claim 62.

The claims as originally presented were rejected under the doctrine of non-statutory obvious-type double patenting in light of the claims presented in U.S.S.N. 09/371,747, now U.S. Patent No. 6,395,716 ('716). The claims in the '716 patent are not the same as, but overlap with the claims presented herein. Therefore, Applicants enclose a Terminal Disclaimer that disclaims the terminal portion of any patent that issues from this application that extends beyond the term of the '716 patent. To facilitate allowable subject matter, Applicants also enclose a Terminal Disclaimer that disclaims the terminal portion of claims granting on pending applications 09/459,150 and 10/022,276.

Supplemental Information Disclosure Statement

Pursuant to the duty of disclosure under 37 CFR §§ 1.56, 1.97 and 1.98, Applicants cite the publications listed on the accompanying PTO-1449. Copies of all listed references are enclosed. The citation of this information does not constitute an admission of priority or that any cited item is available as a reference, or a waiver of any right the applicant may have under the applicable statutes, Rules of Practice in patent cases, or otherwise.

The Examiner's attention is specifically directed to pending United States Patent Application No. 09/867,110, filed on May 29, 2001, related to methods to treat HDV comprising administering a β-L-2'-deoxynucleosides. In addition, the Examiner's attention is specifically directed to pending U.S. Patent Application Nos. 09/459,105, filed on December 10, 1999 and 10/022,148, filed on December 14, 2001, related to methods to treat HBV comprising administering a β-L-2'-deoxynucleoside prodrug. The Examiner's attention is specifically directed to pending United States Patent Application No. 09/883,033, filed on June 15, 2001, related to methods to treat HBV comprising administering a 3'-prodrugs of 2'-deoxy-β-L-nucleoside.

Applicants enclose a Petition for a One Month Extension of Time to reply, to and including, August 11, 2002. The Commissioner is authorized to charge $110.00 associated with this Petition, as well as any other deficiency to Deposit Account 11-0980.

Respectfully submitted,

Josephine Young
Registration No. 48,308

Date: July 17, 2002

Enclosure: Marked up version of amendment

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Version with Markings to Show Changes Made

In the Specification

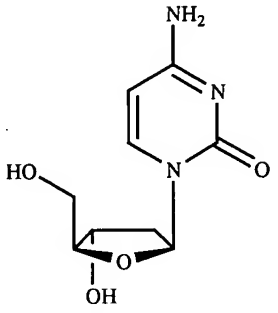
The paragraph on page 1, beginning on line 3, has been amended as follows:

-- This application is a continuation application of U.S. patent application number 09/371,747 filed on August 8, 1999, now **U.S. Patent No. 6,395,716** [~~allowed~~], which claims priority to U.S. provisional application number 60/096,110, filed on August 10, 1998 and U.S. provisional application number 60/131,352, filed on April 28, 1999. --

In the Claims

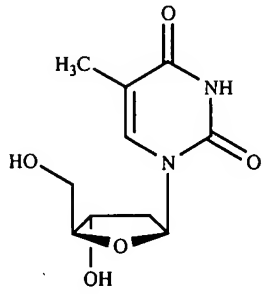
Claims 13-17 and 39-61 have been amended as follows:

13. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a human comprising administering an effective amount of β-L-2'-deoxycytidine of the formula:



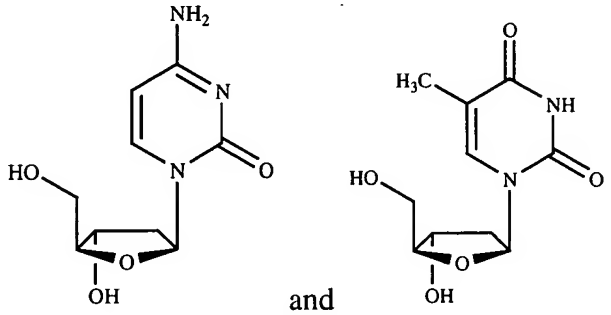
or pharmaceutically acceptable salt thereof.

14. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a human comprising administering an effective amount of β-L-thymidine of the formula:



or pharmaceutically acceptable salt thereof.

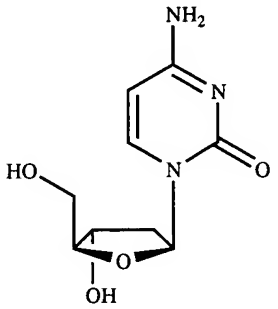
15. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a human comprising administering an effective amount of a combination of the following nucleosides:



and

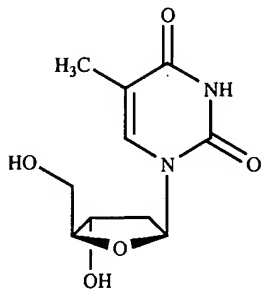
or [a] pharmaceutically acceptable salt thereof.

16. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), **β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine** [~~β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine~~] (L-FMAU), β-D-2,6-diaminopurine dioxolane (DAPD), famciclovir, penciclovir, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.

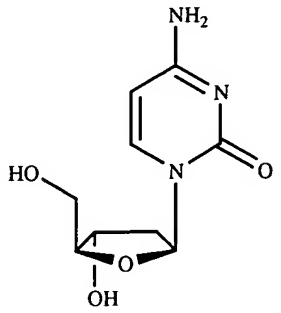
17. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), **β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine** [~~β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine~~] (L-FMAU), β-D-2,6-diaminopurine dioxolane (DAPD), famciclovir, penciclovir, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.

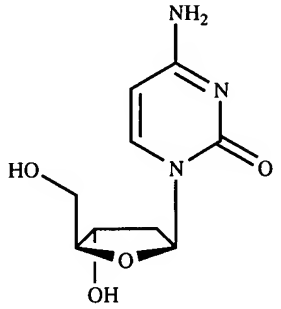
39. (Once Amended, Marked Up) The method of claim **37** [~~28~~] or 38, wherein the dosage unit is a tablet or capsule.

40. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



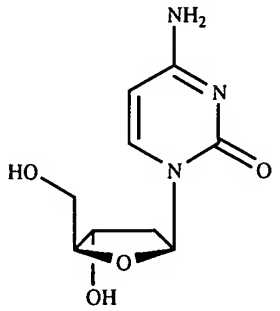
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), or [~~its~~] pharmaceutically acceptable salt thereof.

41. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



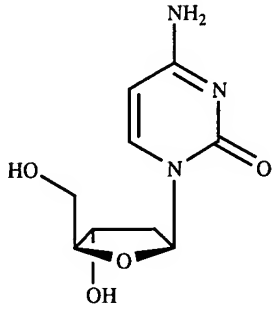
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), or [~~its~~] pharmaceutically acceptable salt thereof.

42. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



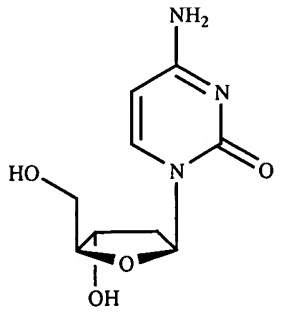
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of **β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine** [~~β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine~~] (L-FMAU), or [~~its~~] pharmaceutically acceptable salt thereof.

43. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



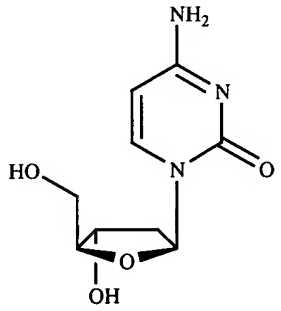
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-D-2,6-diaminopurine dioxolane (DAPD), or [~~its~~] pharmaceutically acceptable salt thereof.

44. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



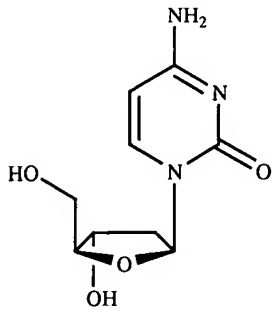
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of famciclovir, or [~~its~~] pharmaceutically acceptable salt thereof.

45. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



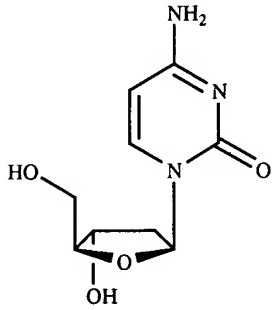
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of penciclovir, or [~~its~~] pharmaceutically acceptable salt thereof.

46. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



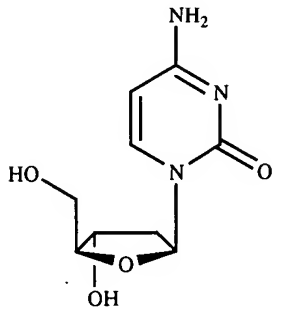
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), or [~~its~~] pharmaceutically acceptable salt thereof.

47. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



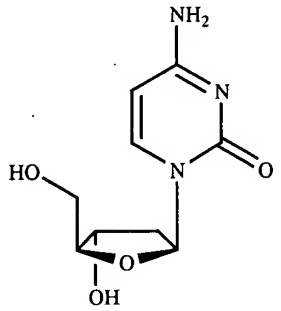
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil), or [~~its~~] pharmaceutically acceptable salt thereof.

48. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



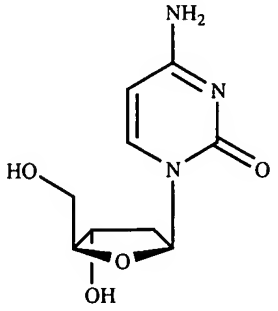
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of lobucavir, or [~~its~~] pharmaceutically acceptable salt thereof.

49. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



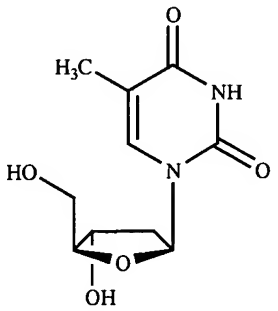
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ganciclovir, or [~~its~~] pharmaceutically acceptable salt thereof.

50. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



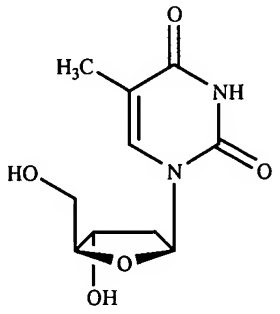
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ribavirin, or [~~its~~] pharmaceutically acceptable salt thereof.

51. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



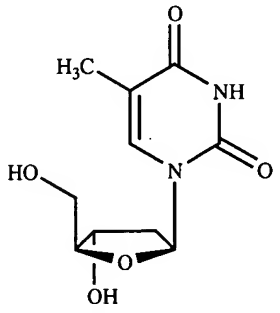
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), or [~~its~~] pharmaceutically acceptable salt thereof.

52. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



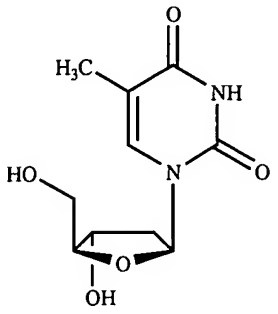
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), or [~~its~~] pharmaceutically acceptable salt thereof.

53. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



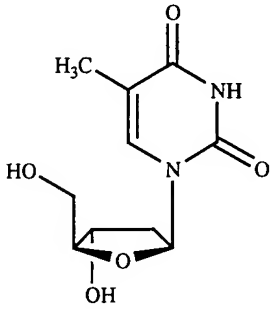
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of **β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine** [~~β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine~~] (L-FMAU), or [~~its~~] pharmaceutically acceptable salt thereof.

54. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



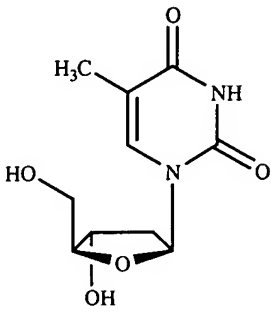
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-D-2,6-diaminopurine dioxolane (DAPD), or [~~its~~] pharmaceutically acceptable salt thereof.

55. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



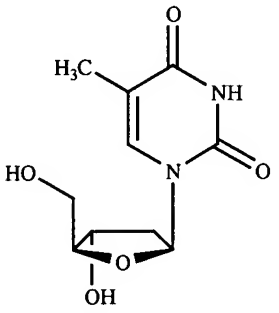
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of famciclovir, or [~~its~~] pharmaceutically acceptable salt thereof.

56. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



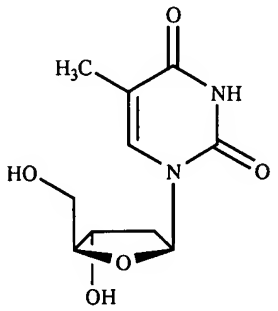
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of penciclovir, or [~~its~~] pharmaceutically acceptable salt thereof.

57. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



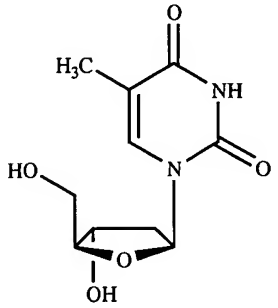
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), or [~~its~~] pharmaceutically acceptable salt thereof.

58. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



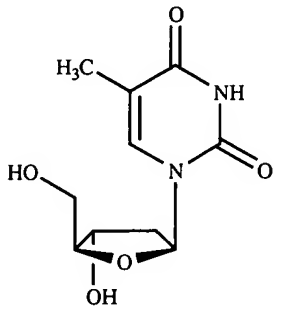
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil), or [~~its~~] pharmaceutically acceptable salt thereof.

59. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



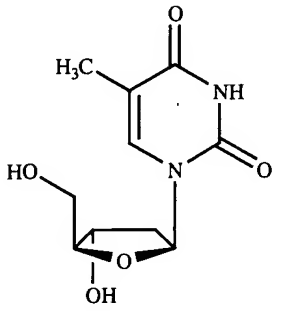
or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of lobucavir, or [~~its~~] pharmaceutically acceptable salt thereof.

60. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ganciclovir, or [~~its~~] pharmaceutically acceptable salt thereof.

61. (Once Amended, Marked Up) A method for the treatment [~~or prophylaxis~~] of a hepatitis B virus infection in a **human** [~~host~~] comprising administering an effective amount of a compound of the formula:



or [~~its~~] pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ribavirin, or [~~its~~] pharmaceutically acceptable salt thereof.